REMARKS

Claims 21 and 35-37 are pending. Claim 21 is currently amended to insert the previously canceled term "pre-diabetic". Support for the amendment is found in the claim as filed. Applicants respectfully requests reconsideration of the present application in view of the reasons that follow.

The Claim objection

The term "pre-diabetic animal" in claim 21 is objected to. This term refers to a disease state in-between a non-diabetic and diabetic animal (see paragraphs **[0036]** and **[0037]** of the application as filed). At such a stage, insulin producing beta cells are still producing sufficient levels of insulin to compensate for glucose levels that are slightly above normal but below the high glucose levels of a diabetic animal, whose beta cells are not able to produce the necessary amounts of insulin (see paragraph **[0003]**). Thus the administration of a candidate agent to a "pre-diabetic animal" can provide meaningful data in the selection of a candidate agent. Withdrawal of the rejection is respectfully requested.

The 35 USC § 103(a) rejection

Claims 21 and 35-37 stand rejected under 35 USC § 103(a) over Meyers et al. (US 2002/0009779), Newgard et al. (US Patent 5,854,067), and Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866).

The rejection in predicated on the argument that since hexokinases are known to play a role in diabetes, one of skill in the art would reasonably expected to be able to use the novel hexokinase taught by Meyers in an assay to identify agents that can be used to treat a diabetic individual. The rejection is respectfully traversed for the following reasons.

1) Aside from the teachings of the present application, only glucokinase is shown to play a role in mediating glucose induced insulin secretion

Hexokinases include hexokinases I, II, III, IV, and V. Hexokinase I-III are also referred to as "low K_m" hexokinases, and hexokinase IV is also referred to as glucokinase. Hexokinases

are present in many cells and are responsible for metabolizing sugars such as glucose, whose cellular uptake is regulated by insulin.

Diabetes is characterized in part by the inability of pancreatic beta cells to produce sufficient amounts of insulin in response to glucose. Yang et al.[1] describes the relationship between pancreatic hexokinases, glucose, and insulin:

> Through a series of remarkable studies, Matschinsky resolved this problem by demonstrating that pancreatic β-cells express an unusual form of hexokinase, called glucokinase. Unlike other hexokinases whose properties are such that glucose metabolism is maximum at about 0.2mM so that higher levels of glucose do not produce higher levels of metabolism, the specific properties of glucokinase allow cells that express glucokinase, including pancreatic β-cells, to metabolize glucose in proportion to plasma levels of glucose when plasma glucose is in the physiological (5-20 mM) range. Key support for the hypothesis that glucokinase serves as a 'glucosensor' was provided by detailed studies which demonstrated that β-cell responses to glucose were in inverse proportion to the degree of inhibition of glucokinase by the high affinity glucokinase inhibitor mannoheptulose [51, 53-56]. Similarly inhibition of glucokinase activity with the low affinity glucokinase inhibitor glucosamine in β-cells also inhibited insulin secretion [57,58].

As summarized in Yang et al., the art thus teaches that only glucokinase regulates insulin secretion and that inhibition of glucokinase *reduces* insulin secretion.[2]

The experimental data disclosed in Liang et al. also supports the finding that of all the pancreatic hexokinases (Liang's experiments involved whole rat pancreatic cells), it is *only* glucokinase that was found to regulate glucose induced insulin secretion. None of the other hexokinases, while present in the pancreatic cells, were found to regulate insulin secretion at physiological glucose concentrations because of their greater affinity (lower K_m) for glucose.

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[1] Yang et al. "A Glucokinase/AP-1 Glucose Transduction Mechanism in the Ventromedial Hypothalamic Satiety Center". Matschinsky FM, Magnuson MA (eds): Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics. Front Diabetes. Basel, Karger, 2004, vol 16, pp 313-326. See page 318. A copy of the reference is included in the supplemental IDS filed with this response.

[2] In fact, glucokinase activators (GKA), compounds that activate rather inhibit glucokinase, are currently touted as potential anti-diabetic agents for enhancing insulin secretion.

2) Meyers et al. does not provide any factual evidence tying hexokinase V expression to pre-diabetes or diabetes, nor does Meyers et al. provide any reasons why inhibiting hexokinase V would be beneficial in treating these disorders

Particularly, Meyers et al. does not provide any factual evidence regarding the existence or expression levels of hexokinase V in pancreatic cells, the role of hexokinase V in such cells if present, the role of hexokinase V in pre-diabetic / diabetic pancreatic cells, or the effect on insulin levels of inhibiting hexokinase V in such cells. Absent such a showing, no conclusion can be drawn linking hexokinase V to glucose-induced insulin secretion in pre-diabetic or diabetic pancreatic cells. Without such a link, there can be no reasonable expectation that inhibiting hexokinase V will result in enhanced glucose-induced insulin secretion as in the claimed method.

3) Newgard does not teach the desirability of inhibiting low K_m hexokinases in patients and instead teaches inhibiting low K_m hexokinases in artificial replacement cells to solely to address the unique limitations of such cells

Newgard teaches inhibiting low K_m hexokinases in artificial insulin producing beta cells that are to be implanted into patients who are unable to produce normal levels of insulin. Newgard teaches that it is well known that in engineering artificial beta cells, the activity levels of low K_m hexokinases are higher than that in normal cells, resulting in increased insulin secretion (column 11, lines 31-36 and column 19, lines 1-27). To obtain cells suitable for use as replacement beta cells, Newgard teaches inhibiting these low K_m hexokinases to *lower* insulin secretion. Such teachings clearly apply to the design of artificial cells and not to the direct treatment of patients with hexokinase inhibitors as is claimed.

4) The findings of the present application (see Figures 1-10) provide evidence of the role of hexokinase V in glucose induced insulin secretion

In particular, Figure 10 shows the unexpected finding that overexpression of hexokinase V results in a decrease in insulin secretion as a response to glucose stimulation. This result suggests that inhibition of hexokinase V in pancreatic cells can result in *increased* insulin secretion. Such findings are contrary to the objective of Newgard where inhibition of

hexokinases in artificial cells is intended to *lower* insulin secretion levels, and also contrary to the observation in Yang et al. *supra* that inhibition of glucokinase *lowers* insulin secretion.

These findings are neither taught nor suggested by Meyers et al., Newgard et al., or Liang et al. either alone or in combination.

For the reasons stated, withdrawal of the rejection under 35 USC § 103(a) of Claims 21 and 35-37 is respectfully requested.

Applicants respectfully submit that all pending rejections have been addressed and that the present application is now in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested. If the Examiner believes a telephone conversation would help advance prosecution of the present application, the Examiner is cordially invited to contact the undersigned at the number below.

Respectfully submitted,

Date October 2, 2008

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